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(54) Title: PROCESS FOR PREPARING NONRACEMIC CHIRAL ALCOHOLS

(57) Abstract: The present invention provides a catalyst system and a process for the preparation of a nonracemic chiral alcohol by hydrogenation of a ketone using the catalyst system, wherein the catalyst system comprises ruthenium, a nonracemic nonatropisomeric chiral diphosphine ligand, an achiral diamine ligand, and a base.

PROCESS FOR PREPARING NONRACEMIC CHIRAL ALCOHOLS

FIELD OF THE INVENTION

This invention relates generally to preparing nonracemic chiral alcohols. It more particularly relates to preparing nonracemic chiral alcohols by hydrogenation of ketones using transition metal catalysts comprising nonracemic chiral ligands. Nonracemic chiral alcohols are useful as pharmaceuticals and other bioactive products and as intermediates for the preparation of such products.

BACKGROUND OF THE INVENTION

Ketones can be converted to racemic chiral alcohols by hydrogenation using certain catalyst systems of ruthenium, a phosphine ligand, a 1,2-diamine, and an alkaline base. Aromatic and heteroaromatic ketones can be hydrogenated to nonracemic chiral alcohols by using certain catalyst systems of ruthenium, certain enantiomeric atropisomeric biaryl diphosphine, an enantiomeric 1,2-diamine, and an alkaline base. *Angew. Chem. Int. Ed.*, vol. 40, (2001), 40-73; U.S. Patent No. 5,763,688; *J. Am. Chem. Soc.*, vol. 117 (1995), 2675-2676. Others have noted that such ketones can be hydrogenated to nonracemic chiral alcohols using related catalyst systems formed with a racemic chiral 1,2-diamine. In their catalyst system, the active diastereomeric ruthenium catalyst is formed with the enantiomeric atropisomeric diphosphine ligand and the "matched" enantiomer of the racemic chiral 1,2-diamine. Interestingly, the diastereomeric ruthenium complex with the "unmatched" enantiomer of the racemic chiral 1,2-diamine, if it is formed, is relatively inactive. *Angew. Chem. Int. Ed.*, vol. 40, (2001), 40-73; European Patent Application 901 997; *J. Am. Chem. Soc.*, vol. 120 (1998), 1086-1087. A catalyst system of ruthenium, the atropisomeric diphosphine (*S*)-2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (*S*-BINAP), achiral ethylene diamine, and potassium hydroxide in isopropanol was reported to hydrogenate 1'-acetonaphthone to (*R*)-1-(1-naphthyl)ethanol in 57% enantiomeric excess. The corresponding catalyst system having enantiomeric (*S,S*)-1,2-diphenylethylenediamine instead of achiral ethylene diamine was reported to hydrogenate 1'-acetonaphthone under the same conditions to (*R*)-1-(1-naphthyl)-ethanol in 97% enantiomeric excess. *Angew. Chem. Int. Ed.*, vol. 40, (2001), 40-73; *J. Am. Chem. Soc.*, vol. 117 (1995), 2675-2676.

Aromatic ketones were similarly hydrogenated to nonracemic chiral alcohols by using a catalyst systems of ruthenium, an enantiomer of 2,2'-bis(diphenylphosphino)-1,1'-dicyclopentane (a diphosphine ligand comprising stereogenic carbon atoms in the bridge between the phosphorus atoms), certain enantiomeric 1,2-diamines, and potassium hydroxide in isopropanol. *J. Org. Chem.*, vol. 64 (1999), 2127-2129.

Atropisomers do not comprise a stereogenic atom, but are chiral because of greatly hindered or prevented rotation about a single bond. In the art, stererogenic atoms are sometimes called asymmetric atoms. Atropisomeric biaryl diphosphine ligands comprise a 1,1'-biaryl bond in the bridge between the phosphorus atoms, about which rotation is sterically prohibited and which are thereby chiral although lacking a stereogenic carbon or phosphorus atom. Examples of atropisomeric biaryl diphosphine ligands include, among others, the enantiomers of 2,2'-bis(diphenylphosphino)1,1'-binaphthyl (BINAP), BINAP derivatives having one or more alkyl or aryl groups connected to one or both naphthyl rings, BINAP derivatives having one to five alkyl substituents on the phenyl rings bonded to phosphorus, for example 2,2'-bis-(di-p-tolylphosphino)-1,1'-binaphthyl (TolBINAP), 5,6,7,8,5',6',7',8'-octahydro-BINAP (H_8BINAP), 2,2'-bis(dicyclohexylphosphino)-6,6'-dimethyl-1,1'-biphenyl (BICHEP) , 2,2'-bis(diphenylphosphino)-6,6'-dimethyl-1,1'-biphenyl (BIPHEMP), 2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl (MeOBIPHEP), [6,6'-(alkylene-α,ω-dioxy)biphenyl-2,2'-diyl]bis(diphenylphosphine) (Cn-TunaPhos; n=1,2,3,... for alkylene=methylene, 1,2-ethylene, 1,3-propylene,... , respectively), 5,5'-bis(diphenylphosphino)-4,4'-bi(benzodioxolyl) (SEGPHOS), and 2,2'-bis(diphenylphosphino)-3,3'-bi(benzo[b]thiophene) (BITIANP).

An attempt to provide a catalyst system of ruthenium, the atropisomeric diphosphine *S*-BINAP, enantiomeric (*S,S*)-1,2-diphenylethylenediamine, and 1,8-diazabicyclo[5.4.0]undec-7-ene as the base (in the place of the alkali base used in the references discussed above) gave no catalytic activity for the hydrogenation of acetophenone. The addition of selected alkali salts of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate to this attempted catalyst system provided catalytic activity for the hydrogenation of acetophenone to nonracemic 1-phenethanol. The investigators conclude that alkali metal cations are required for the activity of this catalyst system. *Angew. Chem. Int. Ed.*, vol. 40, (2001), 3581-3585.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a catalyst system and a process for the preparation of a nonracemic chiral alcohol by hydrogenation of a ketone using the catalyst system, wherein the catalyst system comprises ruthenium, a nonracemic nonatropisomeric chiral diphosphine ligand, preferably comprising a stereogenic carbon atom, an achiral diamine ligand, and a base. Surprisingly, a chiral diamine ligand is not required to obtain highly enantioselective hydrogenation of a ketone to a nonracemic chiral alcohol when using the catalyst system provided above. Accordingly, the present invention also provides methods for the highly enantioselective hydrogenation of a ketone to a nonracemic chiral alcohol using an achiral diamine ligand, with a catalyst system also comprising ruthenium, a nonracemic nonatropisomeric chiral diphosphine ligand, preferably comprising a stereogenic carbon atom, and a base.

In one group of embodiments the base is selected from alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

As used herein, the term "treating", "contacting" or "reacting" refers to adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product. "Side-reaction" is a reaction that does not ultimately lead to a production of a desired product.

"Alkyl" means a linear saturated monovalent hydrocarbon radical or a branched saturated monovalent hydrocarbon radical or a cyclic saturated monovalent hydrocarbon radical, having the number of carbon atoms indicated in the prefix. For example, (C_1-C_6)alkyl is meant to include methyl, ethyl, *n*-propyl, 2-propyl, *tert*-butyl, pentyl, cyclopentyl, cyclohexyl and the like. For each of the definitions herein (*e.g.*, alkyl, alkenyl, alkoxy, aralkyloxy), when a prefix is not included to indicate the number of main chain carbon atoms in an alkyl portion, the radical or portion thereof will have twelve or fewer main chain carbon atoms. A divalent alkyl radical refers to a linear

saturated divalent hydrocarbon radical or a branched saturated divalent hydrocarbon radical having the number of carbon atoms indicated in the prefix. For example, a divalent (C_1-C_6)alkyl is meant to include methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

"Alkenyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix and containing at least one double bond. For example, (C_2-C_6)alkenyl is meant to include, ethenyl, propenyl, and the like.

"Alkynyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical containing at least one triple bond and having the number of carbon atoms indicated in the prefix. For example, (C_2-C_6)alkynyl is meant to include ethynyl, propynyl, and the like.

"Alkoxy", "aryloxy", "aralkyloxy", or "heteroaralkyloxy" means a radical -OR where R is an alkyl, aryl, aralkyl, or heteroaralkyl respectively, as defined herein, *e.g.*, methoxy, phenoxy, benzyloxy, pyridin-2-ylmethyloxy, and the like.

"Aryl" means a monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 12 ring atoms which is substituted independently with one to four substituents, preferably one, two, or three substituents selected from alkyl, alkenyl, alkynyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino and heteroalkyl. More specifically the term aryl includes, but is not limited to, phenyl, biphenyl, 1-naphthyl, and 2-naphthyl, and the substituted derivatives thereof.

"Aralkyl" refers to a radical wherein an aryl group is attached to an alkyl group, the combination being attached to the remainder of the molecule through the alkyl portion. Examples of aralkyl groups are benzyl, phenylethyl, and the like.

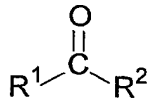
"Heteroalkyl" means an alkyl radical as defined herein with one, two or three substituents independently selected from cyano, alkoxy, amino, mono- or di-alkylamino, thioalkoxy, and the like, with the understanding that the point of attachment of the heteroalkyl radical to the remainder of the molecule is through a carbon atom of the heteroalkyl radical.

"Heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring is optionally substituted independently with one to four substituents, preferably one or two substituents, selected from alkyl, alkenyl, alkynyl, halo, nitro,

cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino and heteroalkyl. More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyridazinyl, pyrimidinyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolinyl, isoquinolyl, benzimidazolyl, benzisoxazolyl or benzothienyl, and the substituted derivatives thereof.

"Hydrocarbyl" is used herein to refer to an organic radical, that can be an alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroalkyl or heteroaryl radical, or a combination thereof which is optionally substituted with one or more substituents generally selected from the groups noted above.

In a general sense, the present invention provides a method for the preparation of a chiral alcohol of formula II (shown without stereochemistry) from a ketone of formula I. Suitable ketones for use in the present invention are those wherein R^1 and R^2 are different, and optionally, one or both of R^1 and R^2 have a chiral center.



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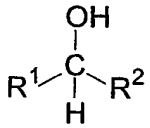


II

The symbols R^1 and R^2 in formulas I and II each independently represent a hydrocarbyl group that can be an acyclic, cyclic, or heterocyclic hydrocarbyl group, or a combination thereof. Additionally, each of the hydrocarbyl groups R^1 and R^2 can be saturated or unsaturated, including components defined above as alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl groups, as well as combinations thereof. Still further, each of R^1 and R^2 can be optionally substituted with one or more substituents that do not interfere with the reaction chemistry of the invention. In some embodiments, R^1 and R^2 are linked together in a cyclic structure. In a preferred combination of R^1 and R^2, R^1 is an optionally substituted alkyl group and R^2 is an optionally substituted aryl or heteroaryl group.

R^1 and R^2 can also be, independently, chiral or achiral. As used herein, however, the adjective "chiral" in the term "chiral alcohol", specifically refers to

the chirality at the carbon atom bearing each of R^1 and R^2, which chirality is produced by the hydrogenation of the keto group at that center. The term is not meant to refer to the chirality that may be present in either R^1 or R^2.

The ruthenium, nonracemic nonatropisomeric chiral diphosphine ligand, and achiral diamine ligand components of the catalyst system can be provided to the reaction mixture individually to form the reactive catalyst complex *in situ* or they can be provided as preformed complexes. Preformed complexes of ruthenium with the nonracemic nonatropisomeric chiral diphosphine ligand, or the achiral diamine ligand, or both can be used.

Examples of preformed complexes of the ruthenium with the nonracemic nonatropisomeric chiral diphosphine ligand include complexes represented by the formula RuX_2LY_n, wherein X represents a halogen atom or pseudo-halide group, preferably chloride or bromide, L represents the nonracemic nonatropisomeric chiral diphosphine ligand, Y represents a weakly coordinating neutral ligand, and n is an integer from 1 to 5. Examples of Y include trialkylamines, for examples triethylamine and tetramethylethylenediamine, and tertiary amides, for example dimethylformamide. Such complexes can be prepared by the reaction of the diphosphine ligand with a complex of the formula $[RuX_2(arene)]_2$, wherein examples of the arene include benzene, p-cymene, 1,3,5-trimethylbenzene, and hexamethylbenzene, in a solvent comprising Y.

Examples of preformed complexes of the ruthenium with both the nonracemic nonatropisomeric chiral diphosphine ligand and achiral diamine ligand include complexes represented by the formula RuX_2LA, wherein A represents the achiral diamine ligand. Such complexes can be prepared by the reaction of the achiral diamine with a complex of the formula RuX_2LY_n as described above.

The ruthenium component of the catalyst system, whether provided to the reaction mixture separately from the other components or used to form a preformed complex with the nonracemic nonatropisomeric chiral diphosphine ligand, the achiral diamine ligand, or both, can be provided by any ruthenium salt or complex capable of forming the active catalyst system in combination with the diphosphine ligand, the achiral diamine ligand, and the base. This can be determined by routine functional testing for ketone hydrogenation activity and enantioselectivity in the manner shown in the Examples. A preferred source of the ruthenium component is a complex of the formula $[RuX_2(arene)]_2$ as defined above.

Suitable nonracemic nonatropisomeric chiral diphosphine ligands for the present invention are bis-tertiary phosphines of the general formula $R^3R^4PR^aPR^5R^6$, wherein R^3, R^4, R^5, and R^6 are hydrocarbyl radicals, which may be the same or different, and R^a is a hydrocarbyl diradical, any of which may be optionally linked in one or more cyclic structures. Suitable hydrocarbyl groups R^3, R^4, R^5, R^6, and diradicals thereof for R^a, include acyclic, cyclic, and heterocyclic hydrocarbyl groups, include saturated and unsaturated hydrocarbyl groups, include alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl groups, and can be optionally substituted with one or more substituents that do not undesirably affect the reaction chemistry of the invention.

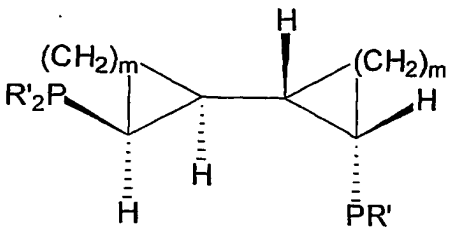
The chirality of the nonracemic nonatropisomeric chiral diphosphine ligand may reside in one or more of the hydrocarbyl groups R^3, R^4, R^5, R^6, in the bridging hydrocarbyl diradical R^a, at phosphorus when two hydrocarbyl radicals on phosphorus are different ($R^3 \neq R^4$, or $R^5 \neq R^6$, or both), or combinations thereof, with the proviso that when the chirality resides solely in the bridging hydrocarbyl diradical R^a, R^a is not an atropisomeric biaryl diradical. When chirality resides in the bridging hydrocarbyl diradical R^a, R^a preferably comprises one or more stereogenic carbon atoms as the source of its chirality. When chirality resides among the hydrocarbyl groups, R^3, R^4, R^5, and R^6, preferably one or more of R^3, R^4, R^5, and R^6 comprises one or more stereogenic carbon atoms in the hydrocarbyl group as the source of chirality. Preferably, atropisomeric chiral substructures are not present in the nonracemic nonatropisomeric chiral diphosphine ligand. Most preferably, the nonracemic nonatropisomeric chiral diphosphine ligand comprises one or more stereogenic carbon atoms.

Illustrative examples of nonracemic nonatropisomeric chiral diphosphine ligands are the enantiomers of 1,2-bis-(diphenylphosphino)propane (PROPHOS), 2,3-bis(diphenylphosphino)butane (CHIRAPHOS), 2,4-bis(diphenyl-phosphino)pentane (SKEWPHOS), 1-cyclohexyl-1,2-bis(diphenylphosphino)ethane (CYCPHOS), 1-substituted 3,4-bis(diphenyl-phosphino)pyrolidine (DEGPHOS), 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP), 3,4-O-isopropylidene-3,4-dihydroxy-2,5-bis(diphenylphosphino)hexane (DIOP*), 1-[1,2-bis-(diphenylphosphino)ferrocenyl]ethyldimethylamine (BPPFA), 1,2-bis[(o-methoxyphenyl)phenylphosphino]ethane (DIPAMP), 2,5-disubstituted 1,2-bis(phospholano)benzenes (DuPHOS), for example 1,2-bis(2,5-dimethyl-phospholano)benzene (Me-DuPHOS), substituted 1,2-bis(phospholano)ethylenes

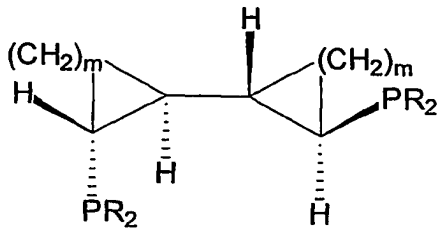
(BPE), for example 1,2-bis(2,5-dimethylphospholano)ethylene (Me-BPE), 1,2-bis-[3,4-benzoxy-2,5-dimethylphospholanyl]benzene (RoPhos), 1,2-bis-[3,4-O-isopropylidene-3,4-dihydroxy-2,5-dimethylphospholanyl]benzene (Me-KetalPhos), 1,1'-bis[3,4-O-isopropylidene-3,4-dihydroxy-2,5-dimethylphospholanyl]ferrocene (Me-f-KetalPhos), 5,6-bis(diphenylphosphino)-2-norbornene (NORPHOS), N,N'-bis-(diphenylphosphino)-N,N'-bis(1-phenylethyl)ethylenediamine (PNNP), 2,2'-bis(diphenylphosphino)-1,1'-dicyclopentane (BICP), 1,2-bis-{2,5-disubstituted-7-phosphabicyclo[2.2.1]hept-7-yl}-benzenes (PennPhos), for example 1,2-bis-{2,5-dimethyl-7-phosphabicyclo[2.2.1]hept-7-yl}-benzene (Me-PennPhos) and 1,2-bis-{2,5-diisopropyl-7-phosphabicyclo[2.2.1]hept-7-yl}-benzene (iPr-PennPhos), and 1,2-bis{1-phosphatricyclo[3.3.0.0]undecan-1-yl}benzene (C5-Tricyclophos), and equivalents thereto that are recognized by those skilled in the art.

Certain preferred nonracemic nonatropisomeric chiral diphosphine ligands comprise at least one, preferably at least two, and most preferably four, stereogenic carbon atoms in the hydrocarbyl diradical that connects the two phosphorus atoms (R^a in the formula above.). Illustrative examples of nonracemic nonatropisomeric chiral diphosphine ligands wherein the bridging hydrocarbyl diradical comprises a stereogenic carbon atom are the enantiomers of PROPHOS, CHIRAPHOS, SKEWPHOS, DIOP, DIOP*, and BICP ligands.

Particularly preferred nonracemic nonatropisomeric chiral diphosphine ligands, wherein the bridging hydrocarbyl diradical comprises a stereogenic carbon atom, comprise a 2,2'-bis-(diorgano-phosphino)-1,1'-bis(cyclic) structure, wherein each cycle of the bridging bis(cyclic) diradical comprises three to eight carbon atoms, and wherein the 1, 1', 2, and 2' carbon atoms in the bis(cyclic) diradical are saturated. These ligands are described in detail in U.S. Patent No. 6,037,500, incorporated herein by reference. The preferred nonracemic diphosphine ligands comprising a 2,2'-bis-(diorgano-phosphino)-1,1'-bis(cyclic) structure are of the formulas III and IV and their enantiomers, in which m=1 to 6 and wherein each cycle of the bis(cyclic) structure may be unsubstituted as shown in formulas III and IV or further substituted with one or more substituents chosen from hydrocarbyl substituents and heteroatom containing substituents that do not interfere with the ketone hydrogenation chemistry, and wherein R' is a substituted or unsubstituted hydrocarbyl group selected from alkyl groups and aryl groups.

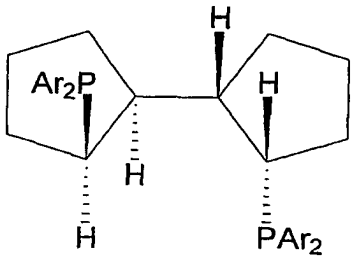


III



IV

Particularly preferred nonracemic nonatropisomeric diphosphine ligands comprising a 2,2'-bis-(diorgano-phosphino)-1,1'-bis(cyclic) structure are of the formula V and its enantiomer, wherein Ar is an aryl group.

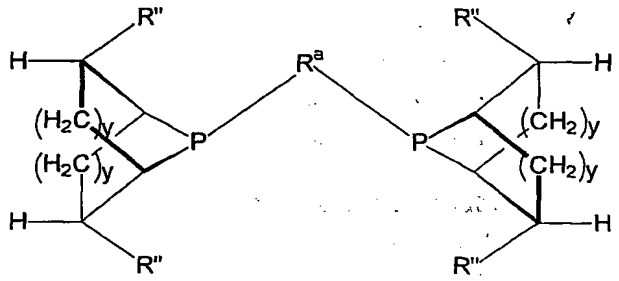


V

Preferred aryl groups in formula V are phenyl (the BICP ligand) and mono-, di-, and trialkyl-phenyl, particularly wherein alkyl is methyl, for example 2,2'-bis[di(3,5-dimethylphenyl)phosphino]-1,1'-dicyclopentane (3,5-Me_8BICP).

Certain other preferred nonracemic nonatropisomeric chiral diphosphine ligands comprise a bis(phosphacyclic) structure, wherein each phosphacycle comprises at least one stereogenic carbon center, preferably at least two. The phosphacyclic structure is selected from phosphamonocyclic structures, preferably phosphacyclopentyl, and phosphabicyclic structures, preferably 7-phosphabicyclo[2.2.1]heptyl. Illustrative examples of nonracemic nonatropisomeric chiral diphosphine ligands comprising a bis(phosphacyclopentyl) structure wherein each phosphacyclopentyl comprises at least one stereogenic carbon atom are the enantiomers of DuPHOS, BPE, C5-Tricyclophos, RoPhos, and KetalPhos. Illustrative examples of nonracemic nonatropisomeric chiral diphosphine ligands comprising a bis(7-phosphabicyclo[2.2.1]heptyl) structure wherein each phosphabicycloheptyl comprises at least one stereogenic carbon atom are the enantiomers of PennPhos ligands.

Particularly preferred nonracemic nonatropisomeric chiral diphosphine ligands comprising a bis(phosphacyclic) structure, wherein each phosphacycles comprises at least one stereogenic carbon center, are bis(phosphabicyclic) ligands of the formula VI, wherein R^a is a bridging hydrocarbyl diradical as defined above, R" is a substituted or unsubstituted hydrocarbyl group selected from alkyl groups and aryl groups, and y is 1 or 2. These ligands are described in detail in U.S. Patent No. 6,037,500, incorporated herein by reference.



VI

Particularly preferred nonracemic nonatropisomeric diphosphine ligands comprising a bis(phosphabicyclic) structure are of the formula VI, wherein R" is a (C1-C3)alkyl group and y=1 (the PennPhos ligands), for example 1,2-bis-{2,5-dimethyl-7-phosphabicyclo[2.2.1]hept-7-yl}-benzene (Me-PennPhos) and 1,2-bis-{2,5-diisopropyl-7-phosphabicyclo[2.2.1]hept-7-yl}-benzene (iPr-PennPhos).

Suitable achiral diamine ligands for the present invention are bis-primary amines of the general formula $H_2NR^bNH_2$, wherein R^b is an achiral hydrocarbyl diradical. Preferably, the hydrocarbyl diradical comprises from 3 to 50 carbon atoms, more preferably from 4 to 50 carbon atoms, and most preferably from 6 to 50 carbon atoms. Suitable achiral hydrocarbyl diradicals for R^b include acyclic, cyclic, and heterocyclic hydrocarbyl diradicals, include saturated and unsaturated hydrocarbyl diradicals, include alkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkenyl, and alkynyl diradicals, and can be optionally substituted with one or more substituents that do not interfere with the reaction chemistry of the invention.

The diamine may be achiral by comprising neither atropisomerism nor stereogenic carbon atoms or it may be achiral comprising a *meso* compound. That is, the achiral hydrocarbyl diradical may contain one or more pairs of stereogenic carbon atoms that are related in at least one of its conformations by a plane of symmetry. For

example, while (*S*,*S*)- and (*R*,*R*)-1,2-diphenylethylenediamine are chiral enantiomers, (*S*,*R*)-1,2-diphenylethylenediamine is an achiral *meso* compound.

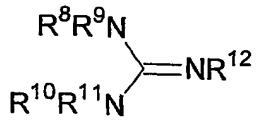
Illustrative examples of achiral diamine compounds comprising at least three carbon atoms include 1,3-propylenediamine, 2-methyl-1,2-propylene-diamine, *meso*-2,3-butanediamine, *meso*-1,2-cyclopentanediamine, *meso*-1,2-cyclo-hexane-diamine, *meso*-1,2-cyclo-heptane-diamine, *meso*-1,2-diphenylethylenediamine, *meso*-2,3-dimethyl-butane-1,2-diamine, 1,2-phenylenediamine, 2-aminobenzyl-amine, 1,8-diaminonaphthalene, and equivalents thereto that are recognized by those skilled in the art, any of which may be substituted with one or more substituents that do not interfere with the reaction chemistry of the invention, and provided such substitution preserves the achirality of the diamine.

Preferred achiral diamines are selected from 1,2-alkylenediamine compounds, 1,2-phenylenediamine compounds and 1,8-diamino-naphthalene compounds, which may be substituted or unsubstituted. Suitable substituents include alkyl (e.g. 4,5-dimethyl-1,2-phenylene-diamine), benzo (e.g. 9,10-diaminophenanthrene), and alkoxy (e.g, 1,3-benzodioxole-5,6-diamine).

Suitable bases include basic inorganic and organic salts, preferably selected from basic salts comprising a cation selected from an alkali metal cation, an alkaline earth cation, and quaternary ammonium cation and a basic anion selected from hydroxide and alkoxide anions. Examples include lithium, sodium, potassium, and quaternary ammonium salts of hydroxide, methoxide, ethoxide, isopropoxide, and t-butoxide.

In a further inventive embodiment of the invention, the base is selected from alkylguanidines, aminophosphazenes, proazaphosphatranes, and alkylamidines. In this embodiment, the base is preferably selected from alkylguanidines, aminophosphazenes, and proazaphosphatranes. In this embodiment, the base is most preferably selected from alkylguanidines.

Suitable alkylguanidines have the general formula VII, wherein R^8, R^9, R^{10}, R^{11}, and R^{12} are independently selected from hydrogen and alkyl groups, with the proviso that at least one of R^8, R^9, R^{10}, R^{11}, and R^{12} is an alkyl group.



VII

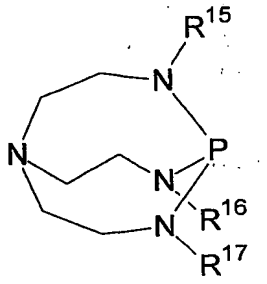
Preferably the alkylguanidine comprises two alkyl groups, more preferably three alkyl groups, even more preferably four alkyl groups, and most preferably five alkyl groups. Any of the alkyl groups R^8, R^9, R^{10}, R^{11}, and R^{12} may be optionally linked in one or more cyclic structures. An illustrative example of a suitable tetraalkylguanidine base is 1,5,7-triazabicyclo[4.4.0]dec-5-ene and tetramethylguanidine. Illustrative examples of suitable pentalkylguanidines are 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene and tetramethyl-2-t-butylguanidine.

Suitable aminophosphazenes have the general formula VII, wherein R^{13} is selected from hydrogen and alkyl groups, R^{14} is an alkyl group and the two R^{14} groups on each $-NR^{14}$ group may optionally be linked in a cyclic structure, and x is an integer from zero to three.

$$R^{13}N{=}P(-NR^{14}{}_2)_x[-N{=}P(NR^{14}{}_2)_3]_{(3-x)} \qquad \text{VIII}$$

Illustrative examples of suitable aminophosphazenes include N,N,N',N',N'',N''-hexa-methyl-phosphorimidic triamide (R^{13}=H, R^{14}=methyl, x=3), N'''-t-butyl-N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide (R^{13}=t-butyl, R^{14}=methyl, x=3), (t-butyl-imino)-tris(pyrrolidino)-phosphorane (R^{13}=t-butyl, $-NR^{14}{}_2$=pyrrolidino, x=3), N'''-[N-ethyl-P,P-bis-(dimethyl-amino)phosphinimyl]-N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide (R^{13}=ethyl, R^{14}=methyl, x=2), and t-butyl-tris[tris(dimethyl-amino)-phosphoranylidene]phosphorimidic triamide (R^{13}=t-butyl, R^{14}=methyl, x=0).

Suitable proazaphosphatranes are described in U.S. Patent No. 5,051,533 and have the general formula IX, wherein R^{15}, R^{16}, and R^{17} are independently selected from hydrogen and alkyl groups.

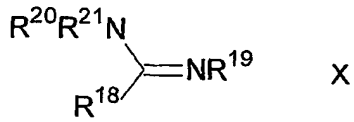


IX

Preferably R^{15}, R^{16}, and R^{17} are selected from C_1 to C_8 alkyl groups,

most preferably methyl. An illustrative preferred proazaphosphatrane is 2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (R^{15}=R^{16}=R^{17}=methyl).

Suitable alkylamidines have the general formula X wherein R^{18}, R^{19}, and R^{20} are independently selected from alkyl groups and R^{21} is selected from hydrogen and alkyl groups. Preferably, R^{21} is selected from alkyl groups.



X

Any of the alkyl groups R^{18}, R^{19}, R^{20}, and R^{21} may be optionally linked in one or more cyclic structures. An illustrative example of a suitable alkylamidine base is 1,5-diazabicyclo[4.3.0]non-5-ene.

The components of the catalyst system are each present in a catalytic amount, meaning less than stoichiometric relative to the ketone reactants. The minimum amount of the catalyst system relative to the ketone reactant may depend on the activity of the specific catalyst system composition, the specific ketone to be reacted, the hydrogen pressure, the gas-liquid mixing characteristics of the reaction vessel, the reaction temperature, the concentrations of the reactants and catalyst system components in the solution, and the maximum time allowed for completion of the reaction, and can be readily determined by routine experimentation. In typical embodiments, the mole ratio of the ruthenium component of the catalyst system to the ketone reactant is in the range from about 1/100 to about 1/100,000, preferably in the range from about 1/500 to about 1/10,000.

The mole ratio of the nonracemic nonatropisomeric chiral diphosphine ligand to the ruthenium in the catalyst system is typically in the range from about 0.5 to about 2.0, preferably from about 0.8 to about 1.2, and most preferably is about 1. The mole ratio of the achiral diamine ligand to the ruthenium in the catalyst system is typically in the range from about 1 to about 50, and preferably from about 5 to about 20. The mole ratio of the base to the ruthenium in the catalyst system is typically in the range from about 1 to about 100, and preferably from about 5 to about 50.

The hydrogenation reaction may be conducted without solvent when the ketone itself is a liquid at the reaction temperature and capable of dissolving the catalyst system. More typically, the hydrogenation reaction is conducted in a solvent system that is capable of dissolving the catalyst system and is reaction-inert. The term

solvent system is used to indicate that a single solvent or a mixture of two or more solvents can be used. The term reaction-inert it used to mean that the solvent system does not react unfavorably with the reactants, products, or the catalyst system. It does not mean that the solvent does not participate productively in the desired reaction. For example, while not wishing to be bound by theory, it is believed that when the base is selected from alkylguanidines, aminophosphazenes, or proazaphosphatranes and the solvent is selected from alcohol solvents, the alcohol solvent levels the base. That is, these bases deprotonate the alcohol to form an alkoxide base in the reaction solution.

The solvent system need not bring about complete solution of the ketone reactant or the chiral alcohol product. The ketone reactant may be incompletely dissolved at the beginning of the reaction or the chiral alcohol product may be incompletely dissolved at the end of the reaction, or both.

Representative solvents are aromatic hydrocarbons such as benzene, toluene, xylene; aliphatic hydrocarbons such as pentane, hexane, heptane; halogen-containing hydrocarbon solvents such as dichloromethane and chlorobenzene; alkyl ethers, polyethers, and cyclic ethers such as methyl-t-butyl-ether, dibutylether, diethoxymethane, 1,2-dimethnoxyethane, and tetrahydrofuran; ester solvents such as ethyl acetate, organic solvents containing heteroatoms such as acetonitrile, DMF and DMSO; and alcohol solvents such as methanol, ethanol, 2-propanol, t-butanol, benzyl alcohol and the like; and mixtures thereof. Preferably, the solvent system comprises an alcohol solvent. Most preferably, the alcohol solvent is 2-propanol.

In typical embodiments, the reaction is suitably conducted at a temperature from about -30°C to about 100°C, more typically from about 0°C to about 50°C, and most typically from about 20°C to about 40°C.

The terms "hydrogenating" and "hydrogenation" refer to reacting the ketone with a source of hydrogen atoms under appropriate conditions so that two hydrogen atoms are added to the carbonyl group of the ketone to produce the hydroxyl group of the chiral alcohol. The source of hydrogen atoms may be molecular hydrogen (H_2), a hydrogen donating organic or inorganic compound, or mixtures thereof. Preferably the source of hydrogen atoms includes molecular hydrogen. Hydrogen donating compounds are compounds capable of donating hydrogen atoms via the action of the catalyst system. Compounds capable of donating hydrogen atoms for transfer hydrogenation reactions using ruthenium catalysts are known in the art, and include alcohols such as methanol, ethanol, *n*-propanol, isopropanol, butanol and

benzyl alcohol, formic acid and salts thereof, unsaturated hydrocarbons and heterocyclic compounds having in part a saturated C-C bond such as tetralin, cyclohexane, and cyclohexadiene, hydroquinone, phosphorous acid, and the like. Among hydrogen donating compounds, alcohols are preferred and isopropanol is most preferred.

The hydrogen pressure in the reaction is typically at least about 1 atm., and typically in the range from about 1 atm. to about 100 atm. More typically, the hydrogen pressure is in the range from about 5 atm to about 20 atm.

The reaction rate and time to completion are dependent on the identities of the ketone reactant and the catalyst components, their absolute concentrations and relative ratios, the temperature, the hydrogen pressure, the gas-liquid mixing provided, and the other reaction conditions. Typically, the reaction is allowed to continue for sufficient time to complete the conversion of the ketone reactant. For typical ketone reactants, using the preferred catalyst systems described and the preferred reaction conditions described herein, the reaction is typically completed in a period of time in the range from about a few minutes to about 24 hours, more typically in the range from about 1 hour to about 10 hours.

The nonracemic chiral alcohol product has, by definition, a stereomeric excess greater than zero. In preferred embodiments, the nonracemic chiral alcohol is formed in at least about 50% stereomeric excess, more preferably at least about 60%, still more preferably at least about 70%, still again more preferably at least about 80%, and most preferably at least about 90%. These stereomeric excesses refer to the chirality at the hydroxyl-bearing carbon of the alcohol group generated by the hydrogenation of the ketone group. When the ketone is achiral, the chiral alcohol can be one of two enantiomers, and the enantiomer excess (e.e.) is the measure of stereomeric excess. When the ketone reactant is already chiral, the chiral alcohol product is a diastereomer, and diastereomeric excess (d.e.) is the formally appropriate measure of stereomeric excess. Accordingly, the term "nonracemic diastereomer" when used to refer to a nonracemic chiral alcohol product, refers to a product with an excess of one diastereomer vs. its diastereomer with the opposite chirality at the hydroxyl-bearing carbon. Preferably, the nonracemic diastereomer is produced in at least about 50% d.e., more preferably at least about 60% d.e., still more preferably at least about 70% d.e., still again more preferably at least about 80% d.e., and most preferably at least about 90% d.e.

EXAMPLES OF THE INVENTION

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following specific examples are intended merely to illustrate the invention and not to limit the scope of the disclosure or the scope of the claims in any way whatsoever.

Preparation 1

Preparation of [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n]: To 7.5 mg (30 microgram-atom Ru) [$RuCl_2$(benzene)]$_2$ and 16.2 mg (32 micromole) (*R*,*R*,*R*,*R*)-2,2'-bis-(diphenylphosphino)-1,1'-dicyclopentane (*R*,*R*,*R*,*R*-BICP) in a 200 ml Schlenk flask under nitrogen was added 10 ml anhydrous, deaerated dimethylformamide (DMF). The resulting orange solution was heated at 130°C for 30 minutes, then evaporated to dryness at 130°C under vacuum (10 mmHg). The resulting orange-red solid residue, comprising [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n], was further dried at 80°C under vacuum for at least an additional hour. A stock solution of 250 micromolar [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n] in isopropanol was prepared by dissolving the solid residue in 120 ml anhydrous, deaerated isopropanol and stored under nitrogen.

This general procedure was used for the preparation of the other [$RuCl_2$(diphosphine)(DMF)n] complexes and the solutions thereof used in the Examples.

Example 1

This Example illustrates the invention wherein acetophenone is hydrogenated to nonracemic 1-phenethanol using a ruthenium catalyst system comprising a nonracemic nonatropisomeric chiral diphosphine ligand, an achiral diamine ligand and an alkoxide base.

In a dry nitrogen-filled glovebox, a 20-ml glass reaction vial was charged with 5 mL 250 micromolar (1.25 micromole) [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n] in isopropanol, 5 mL isopropanol, and 125 microliter 0.1M (12.5 micromole) 4,5-dimethyl-1,2-phenylenediamine in isopropanol. After stirring for several minutes, 73 microliter (625 micromole) acetophenone was added, followed by 0.50 mL 0.1 M (50 micromoles) sodium isopropoxide in isopropanol. The glass reaction vial containing the resulting mixture was sealed in an autoclave, which was then removed from the glovebox. The gas phase in the autoclave was replaced by hydrogen at 18 bar and the reaction mixture was stirred at room temperature for 6 hours under 17-18 bar hydrogen. After

releasing the hydrogen pressure, 1 ml of the resulting reaction solution was eluted through a short column of silica gel with 9 mL methanol. Chiral gas chromatographic analysis of the eluate showed 100% conversion of the acetophenone to give *S*-1-phenethanol with 71% e.e.

Example 2

This Example illustrates the process of the invention wherein acetophenone is hydrogenated to nonracemic 1-phenethanol using a ruthenium catalyst system comprising a nonracemic nonatropisomeric chiral diphosphine ligand, an achiral diamine ligand and an alkylguanidine base.

The procedure was the identical to Example 1 with the exemptions that 0.50 mL 0.1 M (50 micromoles) tetramethyl-2-t-butylguanidine in isopropanol was used instead of the sodium isopropoxide solution. The analysis showed 100% conversion of the acetophenone to give *S*-1-phenethanol with 77% e.e.

Comparative Examples 1 and 2

These Comparative Examples illustrate the hydrogenation of acetophenone to 1-phenethanol using the atropisomeric diphosphine BINAP with an achiral diamine ligand.

The procedures were identical to Examples 1 and 2, respectively, with the exception that an equimolar amount of [$RuCl_2$((*R*,*R*-BINAP)(DMF)n] in isopropanol was substituted for the [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n] solution. The analyses showed, respectively, 100% and 98% conversions of the acetophenone to give *S*-1-phenethanol with 37% and 34% e.e.

By comparison, Examples 1 and 2 show that substantially greater enantioselectivity (about twice as great) is obtained using the nonatropisomeric ligand BICP ligand in combination with the achiral diamine ligand.

Examples 3 and 4

These Examples illustrate the process of the invention wherein 2-acetylthiophene is hydrogenated to nonracemic 1-(2-thienyl)ethanol using a ruthenium catalyst systems comprising a nonracemic nonatropisomeric chiral diphosphine ligand, an achiral diamine ligand and a base.

The procedures were identical to Examples 1 and 2, respectively, with the exceptions that 68 microliter (625 micromole) 2-acetylthiophene reacted

instead of the acetophenone and the reaction mixtures were stirred under hydrogen for 4 hours. The analyses showed 100% conversion of the 2-acetylthiophene to *S*-1-(2-thienyl)ethanol with 84% e.e. in both reactions.

Comparative Example 3

This Comparative Example shows the result of omitting the achiral diamine ligand from the catalyst system.

The procedure was identical to Examples 3 with the exception that the 4,5-dimethyl-1,2-phenylenediamine was omitted and the reaction mixtures were stirred under hydrogen for 10 hours. The analysis showed 3% conversions of 2-acetylthiophene the to give *S*-1-(2-thienyl)ethanol with 37% e.e.

By comparison, Example 3 shows that substantially greater activity (conversion) and enantioselectivity (e.e.) are provided by the catalyst systems comprising an achiral diamine ligand.

Comparative Example 4

This Example shows the result of omitting the base from the catalyst system.

The procedure was identical to Example 3 with the exceptions that the sodium isopropoxide solution was omitted and the reaction mixtures was stirred under hydrogen for 10 hours. The analysis showed only 1% conversion of the ketone.

By comparison, Example 3 shows that the activity for ketone hydrogenation is provided by the catalyst system comprising a base.

Examples 5 and 6

These Examples illustrate the transfer hydrogenation of 2-acetylthiophene to nonracemic 1-(2-thienyl)ethanol using isopropanol as the hydrogen donating compound in the absence of hydrogen.

The procedures were identical to Examples 3 and 4, respectively, with the exception that the reaction mixtures were stirred for 12 hours with a gas phase of nitrogen instead of 4 hours with a gas phase of hydrogen. The analyses showed, respectively, 2% and 3% conversions of the 2-acetylthiophene to *S*-1-(2-thienyl)ethanol with 41% and 24% e.e.

By comparison, Examples 3 and 4 show that the activity of the catalyst system is greater for hydrogenation using molecular hydrogen than for transfer hydrogenation using isopropanol as the sole source of hydrogen atoms.

Examples 7-11 and Comparative Examples 5-7

These Examples illustrate the hydrogenation of 2-acetylthiophene to 1-(2-thienyl)ethanol using various nonatropisomeric chiral diphosphine ligands (Examples 3 and 7-11) and various atropisomeric biaryl diphosphine ligands (Comparative Examples 5-7) with the achiral diamine 4,5-dimethyl-1,2-phenylene-diamine.

Stock solutions of [$RuCl_2$(diphosphine)(DMF)n] complexes were prepared by the procedure described for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n] in Preparation 1. The procedure for the hydrogenation reactions was identical to Example 3 with the exceptions that an equal molar amount the [$RuCl_2$(diphosphine)(DMF)n] having the diphosphine shown in Table 1 (abbreviations are given in the Detailed Description of the Invention) was substituted for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n] and the reaction mixtures were stirred for the time shown in Table 1. Table 1 gives the diphosphine, the reaction time, the conversion of the 2-acetylthiophene, the absolute configuration of the 1-(2-thienyl)ethanol, and its e.e.

Table 1

Example	diphosphine ligand	Time (hours)	Conv. (%)	%e.e. (*R*/*S*)
3	*R*,*R*,*R*,*R*-BICP	4	100	84 (*S*)
7	*R*,*R*-DIOP	12	100	58 (*R*)
8	*R*,*R*-SKEWPHOS	12	100	51 (*S*)
9	*S*,*S*-CHIRAPHOS	10	28	39 (*R*)
10	*R*,*R* -Me-PennPhos	12	14	42 (*S*)
11	*R*,*R* -Me-DuPHOS	6	8	31 (*S*)
Comp. 5	*R* –BINAP	6	77	20 (*S*)
Comp. 6	*R* -C4-TunaPhos	6	68	8 (*R*)
Comp. 7	*S* –MeOBIPHEP	10	84	4 (*S*)

These results show that the exemplified nonatropisomeric chiral diphosphine ligands provide greater enantioselectivities than the comparatively exemplified atropisomeric biaryl diphosphine ligands when used in combination with the achiral diamine ligand 4,5-dimethyl-1,2-phenylenediamine.

Examples 12-17 and Comparative Examples 8-10

These Examples illustrate the hydrogenation of 2-acetylthiophene to 1-(2-thienyl)ethanol using various nonatropisomeric chiral diphosphine ligands (Examples 12-17) and various atropisomeric biaryl diphosphine ligands (Comparative Examples 8-10) with ethylenediamine as the achiral diamine.

The procedure was identical to Example 3 with the exceptions that 125 microliter 0.1M (12.5 micromole) 1,2-ethylene diamine was used instead of the 4,5-dimethyl-1,2-phenylenediamine solution, an equal molar amount the [$RuCl_2$(diphosphine)(DMF)n] having the diphosphine shown in Table 2 was substituted for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n], and the reaction mixtures were stirred for the time shown in Table 2. Table 2 gives the diphosphine, the reaction time, the conversion of the 2-acetylthiophene, the absolute configuration of the 1-(2-thienyl)ethanol, and its e.e.

Table 2

Example	diphosphine ligand	Time (hours)	Conv. (%)	%e.e. (*R*/*S*)
12	*R*,*R*,*R*,*R*-BICP	4	100	56 (*S*)
13	*R*,*R*-DIOP	12	54	42 (*R*)
14	*R*,*R*-SKEWPHOS	6	100	53 (*S*)
15	*S*,*S*-CHIRAPHOS	12	100	43 (*R*)
16	*R*,*R* -Me-PennPhos	12	100	36 (*S*)
17	*R*,*R* -Me-DuPHOS	12	90	54 (*S*)
Comp. 8	*R* –BINAP	4	100	23 (*S*)
Comp. 9	*R* -C4-TunaPhos	6	100	3 (*R*)
Comp. 10	*S* –MeOBIPHEP	12	100	<1 (*R*)

These results show that the exemplified nonatropisomeric chiral diphosphine ligands provide greater enantioselectivities than the comparatively

exemplified atropisomeric biaryl diphosphine ligands when used in combination with ethylenediamine as the achiral diamine ligand.

Examples 18 and 19 and Comparative Examples 11-22

These Examples illustrate the hydrogenation of 2-acetylthiophene to 1-(2-thienyl)ethanol using preferred nonatropisomeric chiral diphosphine ligands and various atropisomeric biaryl diphosphine ligands in combinations with the achiral (*meso*) and chiral stereoisomers of 1,2-cyclohexandiamine.

The procedure was identical to Example 3 with the exceptions that 12.5 micromole of a stereoisomer of 1,2-cyclohexanediamine was substituted for 4,5-dimethyl-1,2-phenylenediamine, an equal molar amount the [$RuCl_2$(diphosphine)(DMF)n] having the diphosphine shown in Table 3 was substituted for [$RuCl_2$(*R,R,R,R*-BICP)(DMF)n], and the reaction mixtures were stirred for the time shown in Table 3. In all these reactions the conversion of the 2-acetylthiophene was 100%. Table 3 gives the diphosphine, the 1,2-cyclohexanediamine stereoisomer, the reaction time, the absolute configuration of the 1-(2-thienyl)ethanol, and its e.e.

Table 3

Example	diphosphine ligand	cyclohexanediamine	Time (hours)	%e.e. (*R*/*S*)
18	*R,R,R,R*-BICP	*meso*	4	81 (*S*)
Comp. 11	*R,R,R,R*-BICP	*R,R*	4	72 (*S*)
Comp. 12	*R,R,R,R*-BICP	*S.S*	6	16 (*S*)
19	*R,R* -Me-PennPhos	*meso*	12	76 (*S*)
Comp. 13	*R,R* -Me-PennPhos	*R.R*	12	63 (*S*)
Comp. 14	*R,R* -Me-PennPhos	*S,S*	12	28 (*R*)
Comp. 15	*R* –BINAP	*meso*	4	45 (*S*)
Comp. 16	*R* –BINAP	*R,R*	4	62 (*S*)
Comp. 17	*R* -C4-TunaPhos	*meso*	6	33 (*S*)
Comp. 18	*R* -C4-TunaPhos	*R,R*	6	40 (*S*)
Comp. 19	*R* -C4-TunaPhos	*S.S*	6	8 (*S*)
Comp. 20	*S* –MeOBIPHEP	*meso*	10	41 (*R*)
Comp. 21	*S* –MeOBIPHEP	*R.R*	10	15 (*R*)
Comp. 22	*S* –MeOBIPHEP	*S,S*	10	47 (*R*)

These results show that preferred nonatropisomeric chiral diphosphine ligands provide greater enantioselectivities than the comparatively exemplified atropisomeric biaryl diphosphine ligands when used in combination with *meso*-1,2-cyclohexanediamine as the achiral diamine ligand. See Examples 18 and 19 vs. Comparative Examples 15, 17, and 20.

These results also show that preferred nonatropisomeric chiral diphosphine ligands provide greater enantioselectivity in combination with the achiral *meso*-stereoisomer of 1,2-cyclohexanediamine than they do in combination with the matched chiral enantiomer. (The "matched" enantiomer is the one that gives greater enantioselectivity than the other.) See Example 18 vs. Comparative Example 11 and Example 19 vs. Comparative Example 13.

In contrast, these results show that the atropisomeric biaryl diphosphine ligands provide greater enantioselectivity in combination with the matched chiral enantiomer of 1,2-cyclohexanediamine than they do in combination with the achiral *meso*-stereoisomer. See Comparative Example 16 vs. Comparative Example 15, Comparative Example 18 vs. Comparative Example 17, and Comparative Example 22 vs. Comparative Example 20.

Additionally, these results show that the combinations of a preferred nonatropisomeric chiral diphosphine ligand with the achiral *meso*-stereoisomer of 1,2-cyclohexanediamine provide greater enantioselectivities that the combinations of the atropisomeric biaryl diphosphine ligands with their matched chiral enantiomer of 1,2-cyclohexanediamine. See Examples 18 and 19 vs. Comparative Examples 16,18, and 22.

Examples 20-32 and Comparative Examples 23-25

These Examples illustrate the hydrogenation of 2-acetylthiophene to 1-(2-thienyl)ethanol using the nonatropisomeric chiral diphosphine ligand BICP (Examples 20-32) and the atropisomeric biaryl diphosphine ligand BINAP (Comparative Examples 23-25) using a various achiral diamine ligands.

The procedure was identical to Example 3 with the exceptions that an equal molar amount of the achiral diamine ligand shown in Table 4 was substituted for the 4,5-dimethyl-1,2-phenylenediamine, for the Comparative Examples an equal molar amount of [$RuCl_2$(*R*-BINAP)(DMF)n] was substituted for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n], and the reaction mixtures were stirred for the time shown in Table 4. Table 4 gives the achiral amine ligand, the diphosphine (BICP or BINAP), the reaction

time, the conversion of the 2-acetylthiophene, the absolute configuration of the 1-(2-thienyl)ethanol, and its e.e.

Table 4					
Example	**achiral diamine**	**diphosphine ligand**	**Time (hrs)**	**Conv. (%)**	**%e.e. (*R*/*S*)**
3	4,5-dimethyl-1,2-phenylenediamine	*R,R,R,R*-BICP	4	100	84 (*S*)
Comp. 5	4,5-dimethyl-1,2-phenylenediamine	*R*-BINAP	6	77	20 (*S*)
12	ethylenediamine	*R,R,R,R*-BICP	4	100	56 (*S*)
Comp. 8	ethylenediamine	*R*-BINAP	4	100	23 (*S*)
18	*meso*-1,2-cyclohexanediamine	*R,R,R,R*-BICP	4	100	81 (*S*)
Comp. 15	*meso*-1,2-cyclohexanediamine	*R*-BINAP	4	100	45 (*S*)
20	*meso*-1,2-diphenylethylenediamine	*R,R,R,R*-BICP	4	100	81 (*S*)
Comp. 23	*meso*-1,2-diphenylethylenediamine	*R*-BINAP	4	96	16 (*S*)
21	1,3-propylenediamine	*R,R,R,R*-BICP	4	100	82 (*S*)
Comp. 24	1,3-propylenediamine	*R*-BINAP	4	100	47 (*R*)
22	1,8-naphthalenediamine	*R,R,R,R*-BICP	4	100	85 (*S*)

Table 4					
Example	**achiral diamine**	**diphosphine ligand**	**Time (hrs)**	**Conv. (%)**	**%e.e. (*R*/*S*)**
Comp. 25	1,8-naphthalenediamine	*R*-BINAP	4	100	65 (*R*)
23	2,2-dimethyl-1,3-propylendiamine	*R,R,R,R*-BICP	6	100	86 (*S*)
24	2-aminobenzylamine	*R,R,R,R*-BICP	6	100	54 (*S*)
25	1,3-pentanediamine	*R,R,R,R*-BICP	6	100	80 (*S*)
26	1,2-phenylenediamine	*R,R,R,R*-BICP	12	100	83 (*S*)
27	4,5-(methylenedioxy)-1,2-phenylene-diamine	*R,R,R,R*-BICP	6	100	81 (*S*)
28	2-aminobenzylamine	*R,R,R,R*-BICP	6	100	54 (*S*)
29	1,4-butanediamine	*R,R,R,R*-BICP	6	14	44 (*S*)
30	2,3-naphthalenediamine	*R,R,R,R*-BICP	12	49	75 (*S*)

Table 4					
Example	**achiral diamine**	**diphosphine ligand**	**Time (hrs)**	**Conv. (%)**	**%e.e. (*R*/*S*)**
31	9,10-phenanthrenediamine	*R,R,R,R*-BICP	6	23	69 (*S*)
32	4-methoxy-1,2-phenylenediamine	*R,R,R,R*-BICP	6	100	82 (*S*)

These results demonstrate that a variety of achiral diamine ligands provide inventive catalyst systems having greater activity than corresponding catalysts system lacking an achiral diamine ligand (by comparison to the conversion in Comparative Example3) and provide nonracemic 1-(2-thienyl)ethanol (e.e.>0). Comparisons between the Examples and the Comparative Examples using the same achiral diamine ligand show that the nonatropisomeric chiral diphosphine ligand BICP consistently provides greater enantioselectivity for the hydrogenation of 2-acetylthiophene than the atropisomeric biaryl diphosphine ligand BINAP.

Examples 33-39 and Comparative Examples 26-28

These Examples illustrate the hydrogenation of acetophenone to 1-phenethanol using the nonatropisomeric chiral diphosphine ligand BICP (Examples 33-39) and the atropisomeric biaryl diphosphine ligand BINAP (Comparative Examples 26-28) using a various achiral diamine ligands.

The procedure was identical to Example 1 with the exceptions that an equal molar amount of the achiral diamine ligand shown in Table 5 was substituted for the 4,5-dimethyl-1,2-phenylenediamine, and for the Comparative Examples an equal molar amount of [$RuCl_2$(*R*-BINAP)(DMF)n] was substituted for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n]. In all these reactions the conversion of the acetophenone was 100%. Table 5 gives the achiral amine ligand, the diphosphine (BICP or BINAP), the absolute configuration of the 1-phenethanol, and its e.e.

Table 5			
Example	**achiral diamine**	**diphosphine ligand**	**%e.e. (*R*/*S*)**
1	4,5-dimethyl-1,2-phenylenediamine	*R,R,R,R*-BICP	71 (*S*)
Comp. 1	4,5-dimethyl-1,2-phenylenediamine	*R*-BINAP	37 (*S*)
33	ethylenediamine	*R,R,R,R*-BICP	51 (*S*)
Comp. 26	ethylenediamine	*R*-BINAP	47 (*S*)
34	*meso*-1,2-cyclohexanediamine	*R,R,R,R*-BICP	67 (*S*)
Comp. 27	*meso*-1,2-cyclohexanediamine	*R*-BINAP	70 (*S*)
35	*meso*-1,2-diphenylethylenediamine	*R,R,R,R*-BICP	73 (*S*)
Comp. 28	*meso*-1,2-diphenylethylenediamine	*R*-BINAP	49 (*S*)
36	*meso*-1,2-di(4-methoxyphenyl)ethylenediamine	*R,R,R,R*-BICP	63 (*S*)
37	1,3-propylenediamine	*R,R,R,R*-BICP	77 (*S*)
38	1,1-dimethyl-1,3-propylenediamine	*R,R,R,R*-BICP	57 (*S*)
39	1,8-naphthalenediamine	*R,R,R,R*-BICP	86 (*S*)

These results demonstrate that a variety of achiral diamine ligands provide inventive catalyst systems for the hydrogenation of acetophenone to nonracemic 1-phenethanol (e.e.>0). Comparisons between the Examples and the Comparative Examples using the same achiral diamine ligand show that the nonatropisomeric chiral diphosphine ligand BICP provides similar (within 5 e.e. percentage points) to substantially greater enantioselectivity than the atropisomeric biaryl diphosphine ligand BINAP.

Examples 40 and 41 and Comparative Examples 29 and 30

These Examples illustrate the hydrogenation of 1'-acetonaphthone to 1-(1-napthyl)ethanol using the nonatropisomeric chiral diphosphine ligand BICP (Examples 40 and 41) and the atropisomeric biaryl diphosphine ligand BINAP (Comparative Examples 29 and 30) in combinations with ethylenediamine and 4,5-dimethyl-1,2-phenylenediamine as achiral diamine ligands.

The procedure was identical to Example 1 with the exceptions that an equal molar amount of 1'-acetonaphthone was substituted for the acetophenone, for Examples 40 and Comparative Example 29 an equal molar amount of ethylenediamine

was substituted for the 4,5-dimethyl-1,2-phenylenediamine, and for the Comparative Examples an equal molar amount of [$RuCl_2$(*S*-BINAP)(DMF)n] was substituted for [$RuCl_2$(*R,R,R,R*-BICP)(DMF)n]. Table 6 gives the achiral amine ligand, the diphosphine (BICP or BINAP), the conversion of the 1'-acetonaphthone, and the absolute configuration of the 1-phenethanol, and its e.e.

Table 6

Example	**achiral diamine**	**diphosphine ligand**	**Conv. (%)**	**%e.e. (*R*/*S*)**
40	ethylenediamine	*R,R,R,R*-BICP	100	66 (*S*)
Comp. 29	ethylenediamine	*S*-BINAP	86	29 (*R*)
41	4,5-dimethyl-1,2-phenylene-diamine	*R,R,R,R*-BICP	25	75 (*S*)
Comp. 30	4,5-dimethyl-1,2-phenylene-diamine	*S*-BINAP	33	20 (*R*)

These results show that, when using an achiral diamine ligand, the nonatropisomeric chiral diphosphine ligand BICP provides substantially greater enantioselectivity than the atropisomeric biaryl diphosphine ligand BINAP.

Examples 42-62

These Examples show the process of the invention for hydrogenation of various ketones to nonracemic chiral alcohols using catalyst systems of the invention.

The procedure was identical to Example 1 with the exceptions that 625 micromole of the ketone shown in Table 7 was reacted instead of the acetophenone, an equal molar amount of 1,8-diaminonaphthalene was substituted for the 4,5-dimethyl-1,2-phenylenediamine, and the reaction mixtures were stirred under hydrogen for the time shown in Table 7. In each example, the analysis showed the conversion of the ketone was 100%. The ketone, the reaction time, the chirality of its nonracemic chiral alcohol product, and its e.e. are given in Table 7.

Table 7			
Example	**ketone**	**Time (hrs)**	**%e.e. (*R*/*S*)**
22	2-acetylthiophene	4	85 (*S*)
39	acetophenone	6	86 (*S*)
42	propiophenone	12	91 (*S*)
43	4'-fluoroacetophenone	9	87 (*S*)
44	4'-isobutylacetophenone	9	89 (*S*)
45	4'-methoxyacetophenone	9	89 (*S*)
46	4'-methylacetophenone	9	88 (*S*)
47	2'-methylacetophenone	9	85 (*S*)
48	2'-methoxyacetophenone	9	79 (*S*)
49	1'-acetonaphthone	9	90 (*S*)
50	2'-acetonaphthone	9	86 (*S*)
51	2-methoxyacetophenone	9	82 (*S*)
52	3-acetylpyridine	9	70 (*S*)
53	2-acetylfuran	9	72 (*S*)
54	2-acetyl-3-methylthiophene	9	84 (*S*)
55	3-acetyl-2,5-dimethylthiophene	9	92 (*S*)
56	3-acetylthiophene	9	87 (*S*)
57	5-bromo-2-acetylthiophene	9	87 (*S*)
58	5-chloro-2-acetylthiophene	9	87 (*S*)
59	5-acetyl-2,4-dimethylthiazole	9	85 (*S*)
60	2-acetylbenzothiophene	9	86 (*S*)
61	methyl isopropyl ketone	9	33 (*R*)
62	methyl isobutenyl ketone	9	66 (*R*)

Examples 63-70

These Examples show the process of the invention for hydrogenation of 2-acetylthiophene to nonracemic 1-(2-thienyl)ethanol using a various bases selected from alkylguanidines and aminophosphazenes with *meso*-cyclohexanediamine as the achiral diamine ligand.

The procedure was identical to Examples 3 and 4 with the exceptions that an equal molar amount of the base shown in Table 8 was substituted for the

sodium isopropoxide (Example 3) or tetramethyl-2-t-butylguanidine (Example 4), an equal molar amount of *meso*-cyclohexanediamine was substituted for the 4,5-dimethyl-1,2-phenylenediamine, and the reaction mixtures were stirred under hydrogen for the time shown in Table 8. Table 8 gives the base, the reaction time, the conversion of the 2-acetylthiophene, and the enantiomeric excess of the *S*-1-(2-thienyl)ethanol product.

Table 8				
Ex. No.	**base**	**Time (hrs)**	**Conv. (%)**	**e.e. (%)**
18	sodium isopropoxide	4	100	81
63	tetramethyl-2-t-butylguanidine	4	84	90
64	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	56	90
65	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	34	91
66	N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide	6	30	90
67	N'''-*t*-butyl-N,N,N',N',N'',N''-hexamethyl-phosphor-imidic triamide	12	100	90
68	(t-butyl-imino)-tris(pyrrolidino)phosphorane	12	100	85
69	N'''-[N-ethyl-P,P-bis(dimethylamino)phosphinimyl]-N,N,N',N',N'',N''-hexamethyl-phosphorimidic triamide	12	100	79
70	t-butyl-tris[tris(dimethylamino)phosphoranylidene]-phosphorimidic triamide	12	100	80

These Examples demonstrate that a variety of bases selected from alkylguanidines and aminophosphazenes provide enantioselectivities at least comparable to that provided by a basic salt (sodium isopropoxide) as the base in the inventive catalyst systems.

Examples 71-79

These Examples show the process of the invention for hydrogenation of 2-acetylthiophene to nonracemic 1-(2-thienyl)ethanol using a various bases selected from alkylamindines, alkylguanidines and aminophosphazenes with ethylene diamine as the achiral diamine ligand.

The procedure was identical to Examples 3 and 4 with the exceptions that an equal molar amount of the base shown in Table 9 was substituted for the sodium isopropoxide (Example 3) or tetramethyl-2-t-butylguanidine (Example 4), an equal molar amount of ethylenediamine was substituted for the 4,5-dimethyl-1,2-phenylenediamine, and the reaction mixtures were stirred under hydrogen for the time shown in Table 9. Table 9 gives the base, the reaction time, the conversion of the 2-acetylthiophene, and the enantiomeric excess of the *S*-1-(2-thienyl)ethanol product.

Table 9

Ex. No.	base	Time (hrs)	Conv. (%)	e.e. (%)
12	sodium isopropoxide	4	100	56
71	tetramethyl-2-t-butylguanidine	6	100	86
72	1,5-diazabicyclo[4.3.0]non-5-ene	12	8	89
73	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	100	88
74	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	95	90
75	N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	6	88	89
76	N"'-*t*-butyl-N,N,N',N',N",N"-hexamethyl-phosphor-imidic triamide	12	100	81
77	(t-butyl-imino)-tris(pyrrolidino)phosphorane	12	100	61
78	N"'-[N-ethyl-P,P-bis(dimethylamino)phosphinimyl]-N,N,N',N',N",N"-hexamethyl-phosphorimidic triamide	12	100	51
79	t-butyl-tris[tris(dimethylamino)phosphoranylidene]-phosphorimidic triamide	6	100	51

These Examples demonstrate that a variety of bases selected from alkylguanidines and aminophosphazenes provide enantioselectivities at least comparable, and in some instances substantially superior to that provided by a basic salt (sodium isopropoxide) as the base in the inventive catalyst systems using ethylenediamine as the achiral diamine ligand.

Examples 80-92

These Examples show the process of the invention for hydrogenation of various ketones to nonracemic chiral alcohols using ethylenediamine as the achiral diamine ligand in combination with either sodium isopropoxide (a basic salt), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (a tetraalkylquanidine base), or tetramethyl-2-t-butylguanidine (a pentaalkylguanidine base).

The procedure was identical to Example 1 with the exceptions that 625 micromole of the ketone shown in Table 10 was reacted instead of the acetophenone, an equal molar amount of ethylenediamine was substituted for the 4,5-dimethyl-1,2-phenylenediamine, for some Examples an equal molar amount of

1,5,7-triazabicyclo[4.4.0]dec-5-ene or tetramethyl-2-t-butylguanidine was substituted for the sodium isopropoxide, and the reaction mixtures were stirred under hydrogen for the time shown in Table 10. In each example, the analysis showed the conversion of the ketone was 100%. Table 10 gives the ketone, the base, the reaction time, and the enantiomeric excess of the *S*-alcohol product.

Table 10

Ex. No.	ketone	base	Time (hrs)	e.e. (%)
12	2-acetylthiophene	sodium isopropoxide	4	56
73	2-acetylthiophene	1,5,7-triazabicyclo[4.4.0]dec-5-ene	6	88
80	2-acetylthiophene	tetramethyl-2-t-butylguanidine	4	86
33	acetophenone	sodium isopropoxide	6	51
81	acetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	83
82	acetophenone	tetramethyl-2-t-butylguanidine	6	77
83	2-acetonaphthone	sodium isopropoxide	9	64
84	2-acetonaphthone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	83
85	2-acetylbenzothiophene	sodium isopropoxide	12	68
86	2-acetylbenzothiophene	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	82
87	2-acetylfuran	sodium isopropoxide	9	60
88	2-acetylfuran	1,5,7-triazabicyclo[4.4.0]dec-5-ene	9	82
89	2-methoxyacetophenone	sodium isopropoxide	9	51
90	2-methoxyacetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	9	75
91	3',5'-bis(trifluoromethyl)acetophenone	sodium isopropoxide	12	78
92	3',5'-bis(trifluoromethyl)acetophenone	1,5,7-triazabicyclo[4.4.0]dec-5-ene	12	76

These Examples show that for many ketones, when using ethylene diamine as the achiral diamine ligand, alkylguanidine bases can provide significantly greater enantioselectivity than a basic salt like sodium isopropoxide. They also show

that the degree of the relative improvement can also depend on the identity of the ketone.

Examples 93-98

These Examples show the process of the invention for hydrogenation of 3-(dimethylamino)-1-(2-thienyl)1-propanone to nonracemic 3-(dimethylamino)-1-(2-thienyl)1-propanol using various achiral diamine ligands and either sodium isoproxide or tetramethyl-2-t-butylguanidine as the base.

A 1.47 mM solution of [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n] in isopropanol was prepared from [$RuCl_2$(benzene)]$_2$ and 1.1 equivalents *R*,*R*,*R*,*R*-BICP following the general procedure given in Preparation 1. For each Example, in a dry nitrogen-filled glovebox, a 20-ml glass reaction vial was charged with 2 mL 1.47 mM (2.9 micromole) [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n] in isopropanol, 3 mL isopropanol, 0.58 mL 0.1M (0.58 mmole) achiral diamine ligand in isopropanol, 0.25 g (1.43 mmole) 3-(dimethylamino)-1-(2-thienyl)1-propanone (free base), and 0.29mL 0.2M (0.58 mmole) base in isopropanol. The glass reaction vial containing the resulting mixture was sealed in an autoclave, which was then removed from the glovebox. The gas phase in the autoclave was replaced by hydrogen and the reaction mixture was stirred under 6.8 bar (gauge) hydrogen at room temperature for 18 hours. The reaction mixture was sampled and analyzed by chiral HPLC. was 100%. Table 10 gives the achiral diamine ligand, the base, the conversion of the ketone, and the enantiomeric excess of the resulting *S*-3-(dimethylamino)-1-(2-thienyl)1-propanol product.

Table 11				
Ex. No.	**achiral diamine ligand**	**base**	**Conv. (%)**	**e.e. (%)**
93	ethylene diamine	sodium isopropoxide	96	24
94	ethylene diamine	tetramethyl-2-t-butylguanidine	89	79
95	2-methyl-1,2-propylenediamine	sodium isopropoxide	97	68
96	2-methyl-1,2-propylenediamine	tetramethyl-2-t-butylguanidine	85	85
97	meso-1,2-cyclohexanediamine	sodium isopropoxide	96	83
98	meso-1,2-cyclohexanediamine	tetramethyl-2-t-butylguanidine	77	88

These Examples further show that an alkylguanidine base can provide significantly greater enantioselectivity than a basic salt like sodium isopropoxide. They also show that the degree of the relative improvement can also depend on the identity of the achiral diamine ligand, and appears greatest with a simpler and smaller achiral diamine, especially with ethylene diamine.

Comparative Examples 30 and 31

These Comparative Examples illustrate the hydrogenation of hydrogenation of 3-(dimethylamino)-1-(2-thienyl)1-propanone to nonracemic 3-(dimethylamino)-1-(2-thienyl)1-propanol using the atropisomeric biaryl diphosphine ligands BINAP and MeOBIPHEP in combination with the achiral diamine ligand ethylenediamine and the base tetramethyl-2-t-butylguanidine.

The procedure was identical to Example 94 with the exception that an equal molar amount of [$RuCl_2$(*R*-BINAP)(DMF)n] or [$RuCl_2$(*S*-MeOBIPHEP)(DMF)n] was substituted for [$RuCl_2$(*R*,*R*,*R*,*R*-BICP)(DMF)n]. Table 12 gives the diphosphine ligand, the conversion of the ketone, and chirality of the resulting *S*-3-(dimethylamino)-1-(2-thienyl)1-propanol, and its enantiomeric excess.

Table 12			
Example	**diphosphine ligand**	**Conv. (%)**	**%e.e. (*R*/*S*)**
94	*R*,*R*,*R*,*R*-BICP	89	79 (*S*)
Comp. 30	*R*-BINAP	56	24 (*S*)
Comp. 31	*S*-MeOBIPHEP	73	21 (*R*)

These results show that a preferred nonatropisomeric chiral diphosphine ligand, BICP, provides greater activity and substantially greater enantioselectivity than the atropisomeric biaryl diphosphine ligands when in combination with ethylene diamine, and even when a pentaalkylguanidine is used as the base.

Comparative Examples 32-35

These Examples illustrate the hydrogenation of 3-(dimethylamino)-1-(2-thienyl)1-propanone to nonracemic 3-(dimethylamino)-1-(2-thienyl)1-propanol using the nonatropisomeric chiral diphosphine ligand BICP and the base tetramethyl-2-t-butylguanidine with enantiomeric chiral diamine ligands.

The procedure was identical to Example 94 with the exception that an equimolar amount of the diamine shown in Table 13 was substituted for ethylenediamine. Table 13 gives the diamine ligand, the conversion of the ketone, and the enantiomeric excess of the resulting *S*-3-(dimethylamino)-1-(2-thienyl)1-propanol product (ND=not determined), together with results from comparable Examples using achiral diamine ligands.

Table 12			
Example	**diamime ligand**	**Conv. (%)**	**e.e. (%)**
94	ethylenediamine	89	79
Comp. 32	*R*-1,2-propylenediamine	96	78
Comp. 33	*S*-1,2-propylenediamine	94	49
96	2-methyl-1,2-propylenediamine	85	85
98	*meso*-1,2-cyclohexanediamine	77	88
Comp. 34	*R,R*-1,2-cyclohexanediamine	38	74
Comp. 35	*S,S*-1,2-cyclohexanediamine	<5	ND

By comparison with Example 94, Comparative Example 32 shows that, with a preferred nonatropisomeric chiral diphosphine ligand, *R,R,R,R*-BICP, the addition of a methyl group to ethylenediamine to make the "matched" *R*-enantiomer of 1,2-propylenediamine does not provide any greater enantioselectivity. In contrast, the addition of a second methyl group at the same position to make the achiral 2-methyl-1,2-propylenediamine, in Example 96, does provide greater enantioselectivity.

Comparison of Example 98 with Comparative Example 34 shows that, with *R,R,R,R*- BICP, greater activity and enantioselectivity are obtained with achiral *meso*-1,2-cyclohexanediamine than with the "matched" *R,R*-enantiomer of 1,2-cyclohexanediamine as the diamine ligand.

Example 99

This Example illustrates a preparative scale hydrogenation of 3-(dimethylamino)-1-(2-thienyl)1-propanone to nonracemic 3-(dimethylamino)-1-(2-thienyl)1-propanol according to the process of the invention.

In a dry nitrogen-filled glovebox, a 300 mL autoclave was charged with 20.0 g (109 mmol) 3-(dimethylamino)-1-(2-thienyl)1-propanone (free base), 90 ml isopropanol, 40 mL ethanol, 0.52 mL (4.36 mmol) tetramethyl-2-t-butylguanidine, and 31.1 mL 7.0 mM (0.22 mmol) [$RuCl_2$((*R,R,R,R*-BICP)(DMF)n] in 4:1 isopropanol:dichloromethane. The autoclave was sealed with a head equipped for overhead stirring and removed from the glovebox. The gas phase in the autoclave reactor was replaced by hydrogen and the reaction mixture was stirred under 6.8 bar

(gauge) hydrogen at room temperature for 21 hours. HPLC analysis of a sample of the reaction mixture showed 100% conversion of the ketone. The reaction mixture was concentrated to 50 mL by rotary evaporation (25°C/10 mmHg). The concentrate was diluted with 150 ml heptane and a seed crystal was added. This mixture was concentrated again by rotary evaporation to 50 mL and refrigerated at 4°C overnight. The resulting crystals were collected by filtration, washed with cold heptane and dried under high vacuum to yield 11.9 g (59% yield) *S*-3-(dimethylamino)-1-(2-thienyl)-1-propanol as white prisms. Chiral HPLC analysis showed 99.7% chemical purity and 99.1% e.e.

Example 100

This Example illustrate the process of the invention for the hydrogenation of a enantiomeric chiral ketone to a diastereomeric chiral alcohol.

In a dry nitrogen-filled glovebox, a glass autoclave liner was charged with 20 ml 125 micromolar (2.5 micromoles) [$RuCl_2$((*S*,*S*,*S*,*S*-BICP)(DMF)n] in isopropanol, 90 ml isopropanol, 0.5 ml 0.1 M (50 micromoles) 4,5-dimethyl-1,2-diamino-benzene in isopropanol. After stirring for about 2 minutes, 5.2 g (12.5 millimole) (2*S*)-1-(4-benzyl-oxy-phenyl)-2-(4-hydroxy-4-phenyl-piperidin-1-yl)-1-propanone was added, followed by 0.5 ml 0.2 M (100 micromoles) sodium isopropoxide in isopropanol. The glass liner containing the resulting suspension was sealed in an autoclave, which was then removed from the glovebox. The gas phase in the autoclave was replaced by hydrogen at 18 bar. The gas-liquid mixture was then stirred for 22 hours. Chiral HPLC analysis of the reaction mixture showed 98.8% conversion of the ketone to give (1*S*,2*S*)-1-(4-benzoxyphenyl)-2-(4-hydroxy-4-phenyl-piperidin-1-yl)-1-propanol with 99.1% d.e.

The product was isolated by filtering the resulting suspension, washing the solid with isopropanol (3 x 20 ml), and drying it under vacuum to obtain the product as a white solid in >80% yield, >98% purity, and >99% d.e.

Example 101

This Example illustrates the process of the invention for producing the opposite enantiomer of the diastereomeric chiral alcohol produced in Example 100 by using the opposite enantiomers of the chiral ketone and the diphosphine ligand that were used in Example 100.

(2*R*)-1-(4-benzyl-oxy-phenyl)-2-(4-hydroxy-4-phenyl-piperidin-1-yl)-1-propanone was hydrogenated in isopropanol solution at room temperature under 18

bar hydrogen for one hour at using [$RuCl_2$((*R*,*R*,*R*,*R*-BICP)(DMF)n], 4,5-dimethyl-1,2-diamino-benzene and sodium isopropoxide in the mole ratios ketone:Ru:BICP:diamine:base = 500:1:1:5:20. Chiral HPLC analysis of the reaction mixture showed 98.8% conversion of the ketone to give (1*R*,2*R*)-1-(4-benzoxyphenyl)-2-(4-hydroxy-4-phenyl-piperidin-1-yl)-1-propanol with 98.2% d.e.

This example also illustrates that because the diamine ligand is achiral, the same diamine ligand may be used to prepare either enantiomer of the chiral alcohol.

Example 102

This Example illustrates the process of the invention for producing a diastereomer of the chiral alcohol enantiomers produced in Examples 100 and 101 by using the opposite enantiomer of the chiral ketone used in Example 101, but same enantiomer of the diphosphine ligand used in that Example.

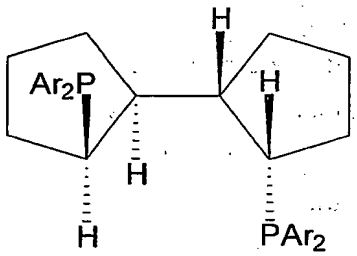
The procedure was identical to Example 101 with the exception that the (2*S*) enantiomer of the 1-(4-benzyl-oxy-phenyl)-2-(4-hydroxy-4-phenyl-piperidin-1-yl)-1-propanone was reacted, again using the (*R*,*R*,*R*,*R*)-BICP ligand. Chiral HPLC analysis of the reaction mixture showed 99.5% conversion of the ketone to give (1*R*,2*S*)-1-(4-benzoxyphenyl)-2-(4-hydroxy-4-phenyl-piperidin-1-yl)-1-propanol with 92.0% d.e.

Examples 101 and 102 taken together show that the chirality generated at the 1-carbon by hydrogenation of this ketone to the alcohol is predominantly controlled by the chirality of the diphosphine ligand, and only relatively weakly influenced by the chirality already present at the 2-carbon of the this ketone. Whether the (2*R*)-ketone (Example 100) or the (2*S*)-ketone (Example 101) is hydrogenated using the (*R*,*R*,*R*,*R*)-BICP ligand, the chirality generated in the alcohol is predominantly (1*R*) by greater than 90% d.e.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

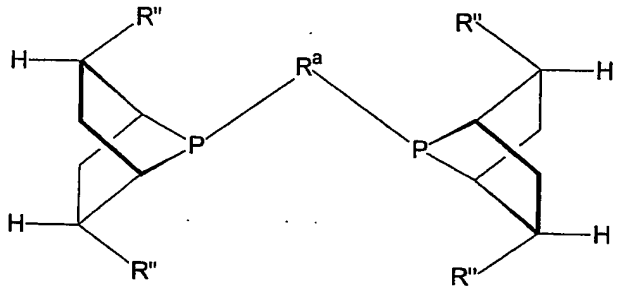
WHAT IS CLAIMED IS

1. Catalyst system useful for the hydrogenation of a ketone to a nonracemic chiral alcohol comprising ruthenium, a nonracemic nonatropisomeric chiral diphosphine ligand, an achiral diamine ligand, and a base.
2. Catalyst system according to claim 1 wherein the nonracemic nonatropisomeric chiral diphosphine ligand comprises at least one stereogenic carbon atom, preferably wherein the nonracemic nonatropisomeric chiral diphosphine ligand comprises at least one stereogenic carbon atom in a hydrocarbyl diradical that connects the two phosphorus atoms, more preferably wherein the nonracemic diphosphine ligand comprises a 2,2'-bis(diorganophosphino)-1,1'-bis(cyclic) structure.
3. Catalyst system according to claim 1 or claim 2 wherein the nonracemic diphosphine ligand is selected from enantiomers of diphosphine ligands having the structural formula



wherein Ar is an aryl group.

4. Catalyst system according to claim 3 wherein Ar is selected from phenyl, monoalkylphenyl, dialkylphenyl, and trialkylphenyl.
5. Catalyst system according to any of claims 1-4 wherein the nonracemic nonatropisomeric chiral diphosphine ligand comprises a bis(phosphacyclic) structure, wherein each phosphacycle comprises at least one stereogenic carbon atom, wherein the phosphacycle is preferably selected from phosphacyclopentyl and 7-phosphabicyclo[2.2.1]heptyl.
6. Catalyst system according to any of claims 1-5 wherein the nonracemic diphosphine ligand is selected from enantiomers of diphosphine ligands having the structural formula



wherein R^a is a hydrocarbyl diradical and R" is a substituted or unsubstituted hydrocarbyl group selected from alkyl groups and aryl groups.

7. Catalyst system according to any of claims 1-6 wherein the achiral diamine ligand is a bis-primary amine ligand, preferably wherein the achiral diamine is selected from *meso*-1,2-alkylenediamine compounds, 1,2-phenylenediamine compounds and 1,8-diaminonaphthalene compounds.

8. Catalyst system according to any of claims 1-7 wherein the base is selected from basic inorganic and organic salts, alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes, preferably selected from alkylamidines, alkylguanidines, aminophosphazenes, and proazaphosphatranes, wherein more preferably the base is an alkylguanidine, wherein most preferably, the base is a pentaalkylguanidine.

9. Process for the preparation of a nonracemic chiral alcohol comprising hydrogenating a ketone in the presence of a catalyst system according to any of claims 1-8.

10. Process according to claim 9 wherein the nonracemic chiral alcohol is formed in at least about 60% stereomeric excess.

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00826

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J31/24 B01J31/18 C07F15/00 C07C29/145 C07B53/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J C07F C07C C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CAO PING ET AL: "Ru-BICP-Catalyzed asymmetric hydrogenation of aromatic ketones" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 64, no. 6, 19 February 1999 (1999-02-19), pages 2127-2129, XP002169915 ISSN: 0022-3263 cited in the application the whole document --- -/--	1-4,7-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2003	16/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goebel, M

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PCT/NL 02/00826

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A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; AKOTSI, OKWADO M. ET AL: "Versatile precursor to ruthenium-bis(phosphine) hydrogenation catalysts" retrieved from STN Database accession no. 133:121957 XP002236692 structure abstract & CHIRALITY (2000), 12(5/6), 514-522 ,	1,2,5, 7-10
A	EP 0 901 997 A (HASEGAWA T CO LTD ;TAKASAGO PERFUMERY CO LTD (JP)) 17 March 1999 (1999-03-17) cited in the application paragraphs '0014!-'0019!; claims 1-3	1,2,5, 7-10
A	NOYORI R ET AL: "ASYMMETRIC CATALYSIS BY ARCHITECTURAL AND FUNCTIONAL MOLECULAR ENGINEERING: PRACTICAL CHEMO- AND STEREOSELECTIVE HYDROGENATION OF KETONES" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 40, no. 1, January 2001 (2001-01), pages 41-73, XP000998801 ISSN: 0570-0833 cited in the application page 44 page 46 page 51 -page 52 page 56	1,2,5-10
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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